

In the Claims

Please amend the claims as follows:

- P.
1. (Currently amended) A method to ~~identify~~ determine or detect an agent that alters adeno-associated virus (AAV) transduction of a mammalian cell, comprising:
 - a) contacting the mammalian cell with an agent and virus; and
 - b) detecting or determining whether the agent ~~alters viral transduction, wherein the agent~~ alters transduction after viral binding to ~~receptors~~ the cell membrane and before synthesis to an expressible form of the viral genome.
 2. (Currently amended) The method of claim 1 or 87 wherein the cell is a mammalian lung cell.
 3. (Currently amended) The method of claim 1 or 87 wherein the cell is a mammalian liver cell.
 4. (Currently amended) The method of claim 1 or 87 wherein the cell is a human cell, canine cell, murine cell, rat cell or rabbit cell.
 5. (Currently amended) The method of claim 1 or 87 wherein the transduction is enhanced.
 6. (Currently amended) The method of claim 1 or 87 wherein the agent enhances endosomal processing.
 7. (Currently amended) The method of claim 1 or 87 wherein the agent is an endosomal protease inhibitor.
 8. (Original) The method of claim 7 wherein the agent is a cysteine protease inhibitor.

AMENDMENT AND RESPONSE UNDER 37 CFR 1.116

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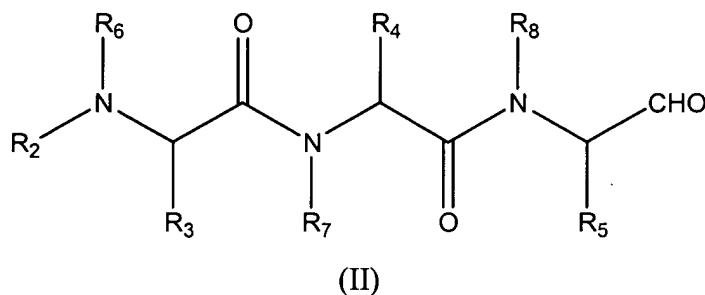
Title: COMPOUNDS AND METHODS TO ENHANCE rAAV TRANSDUCTION

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9. (Currently amended) The method of claim 1 or 87 wherein the agent is a peptide or analog thereof.
10. (Currently amended) The method of claim 1 or 87 wherein the virus is recombinant adeno-associated virus.
11. (Original) The method of claim 10 wherein the recombinant virus encodes a therapeutic peptide or polypeptide.
12. (Previously amended) The method of claim 10 wherein the recombinant virus comprises a marker gene that is detectable or selectable.
- 13-28. (Cancelled)
29. (Currently amended) The method of claim 1, ~~13, 14, 15, 16~~ or ~~17~~, 87 wherein the agent is a compound of formula (I): $R_1-A-(B)_n-C$ wherein R_1 is an N-terminal amino acid blocking group; each A and B is independently an amino acid; C is an amino acid wherein the terminal carboxy group has been replaced by a formyl (CHO) group; and n is 0, 1, 2, or 3; or a pharmaceutically acceptable salt thereof.
30. (Original) The method of claim 29 wherein R_1 is (C_1-C_{10}) alkanoyl.
31. (Original) The method of claim 29 wherein R_1 is acetyl or benzyloxycarbonyl.
32. (Original) The method of claim 29 wherein each A and B is independently alanine, arginine, glycine, isoleucine, leucine, valine, nor-leucine or nor-valine.
33. (Original) The method of claim 29 wherein each A and B is isoleucine.

34. (Original) The method of claim 29 wherein C is alanine, arginine, glycine, isoleucine, leucine, valine, nor-leucine or nor-valine, wherein the terminal carboxy group has been replaced by a formyl (CHO) group.
35. (Original) The method of claim 29 wherein C is nor-leucine or nor-valine, wherein the terminal carboxy group has been replaced by a formyl (CHO) group.
36. (Original) The method of claim 29 wherein R₁ is (C₁-C₁₀)alkanoyl or benzyloxycarbonyl; A and B are each isoleucine; C is nor-leucine or nor-valine, wherein the terminal carboxy group has been replaced by a formyl (CHO) group; and N is 1.
37. (Currently amended) The method of claim 1, ~~13, 14, 15, 16~~ or ~~17~~ or 87 wherein the agent is a compound of formula (II):



wherein

R₂ is an N-terminal amino acid blocking group;

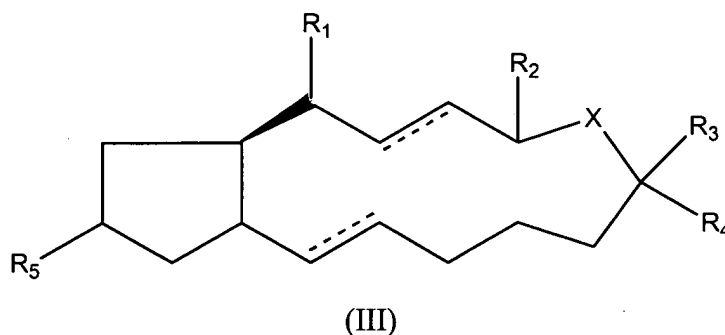
R₃, R₄, and R₅ are each independently hydrogen, (C₁-C₁₀)alkyl, aryl or aryl(C₁-C₁₀)alkyl;

and

R₆, R₇, and R₈ are each independently hydrogen, (C₁-C₁₀)alkyl, aryl or aryl(C₁-C₁₀)alkyl; or a pharmaceutically acceptable salt thereof.

38. (Original) The method of claim 37 wherein R₂ is (C₁-C₁₀)alkanoyl.
39. (Original) The method of claim 37 wherein R₂ is acetyl or benzyloxycarbonyl.

40. (Original) The method of claim 37 wherein R_3 is hydrogen or (C_1-C_{10}) alkyl.
41. (Original) The method of claim 37 wherein R_3 is 2-methylpropyl.
42. (Original) The method of claim 37 wherein R_4 is hydrogen or (C_1-C_{10}) alkyl.
43. (Original) The method of claim 37 wherein R_4 is 2-methylpropyl.
44. (Original) The method of claim 37 wherein R_5 is hydrogen or (C_1-C_{10}) alkyl.
45. (Original) The method of claim 37 wherein R_5 is butyl or propyl.
46. (Original) The method of claim 37 wherein R_2 is acetyl or benzyloxycarbonyl; R_3 and R_4 are each 2-methylpropyl; R_5 is butyl or propyl; and R_6 , R_7 , and R_8 are each independently hydrogen.
47. (Currently amended) The method of claim 1, ~~13, 14, 15, 16~~ or ~~17~~ 87 wherein the agent is a compound of formula (III):



wherein

R_1 is H, halogen, (C_1-C_{10}) alkyl, (C_1-C_{10}) alkenyl, (C_1-C_{10}) alkynyl, (C_1-C_{10}) alkoxy, (C_1-C_{10}) alkanoyl, $(=O)$, $(=S)$, OH, SR, CN, NO_2 , trifluoromethyl or (C_1-C_{10}) alkoxy, wherein any alkyl, alkenyl, alkynyl, alkoxy or alkanoyl may optionally be substituted with one or more

halogen, OH, SH, CN, NO₂, trifluoromethyl, NRR or SR, wherein each R is independently H or (C₁-C₁₀)alkyl;

R₂ is (=O) or (=S);

R₃ is H, (C₁-C₁₀)alkyl, (C₁-C₁₀)alkenyl, (C₁-C₁₀)alkynyl, (C₁-C₁₀)alkoxy or (C₃-C₈)cycloalkyl, wherein any alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl may optionally be substituted with one or more halogen, OH, CN, NO₂, trifluoromethyl, SR, or NRR, wherein each R is independently H or (C₁-C₁₀)alkyl;

R₄ is H, (C₁-C₁₀)alkyl, (C₁-C₁₀)alkenyl, (C₁-C₁₀)alkynyl, (C₁-C₁₀)alkoxy or (C₃-C₈)cycloalkyl, wherein any alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl may optionally be substituted with one or more halogen, OH, CN, NO₂, trifluoromethyl, SR, or NRR, wherein each R is independently H or (C₁-C₁₀)alkyl;

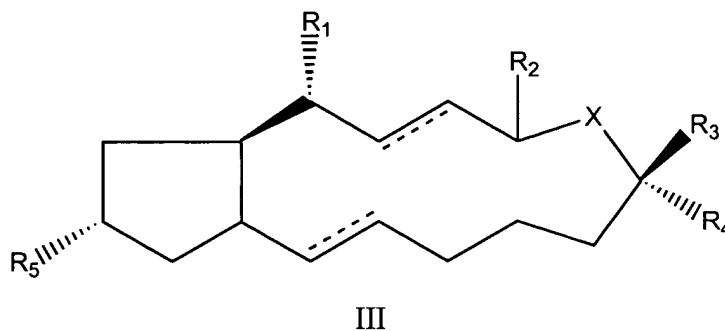
R₅ is H, halogen, (C₁-C₁₀)alkyl, (C₁-C₁₀)alkenyl, (C₁-C₁₀)alkynyl, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkanoyl, (=O), (=S), OH, SR, CN, NO₂ or trifluoromethyl, wherein any alkyl, alkenyl, alkynyl, alkoxy or alkanoyl may optionally be substituted with one or more halogen, OH, SH, CN, NO₂, trifluoromethyl, NRR or SR, wherein each R is independently H or (C₁-C₁₀)alkyl; and

X is O, S or NR wherein R is H or (C₁-C₁₀)alkyl, or a pharmaceutically acceptable salt thereof.

48. (Original) The method of claim 47 wherein R₁ is halogen, CN, NO₂, trifluoromethyl or OH.
49. (Original) The method of claim 47 wherein R₁ is OH.
50. (Original) The method of claim 47 wherein R₂ is (=O).
51. (Original) The method of claim 47 wherein R₃ is H or (C₁-C₁₀)alkyl.
52. (Original) The method of claim 47 wherein R₃ is methyl.

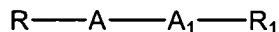
53. (Original) The method of claim 47 wherein R₄ is H or (C₁-C₁₀)alkyl.
54. (Original) The method of claim 47 wherein R₄ is H.
55. (Original) The method of claim 47 wherein R₅ is halogen, CN, NO₂, trifluoromethyl or OH.
56. (Original) The method of claim 47 wherein R₅ is OH.
57. (Original) The method of claim 47 wherein X is O or S.
58. (Original) The method of claim 47 wherein X is O.
59. (Original) The method of claim 47 wherein both ----- are a single bond.
60. (Original) The method of claim 47 wherein one ----- is a double bond.
61. (Original) The method of claim 47 wherein both ----- are a double bond.
62. (Original) The method of claim 45 wherein R₁ is OH, R₂ is (=O), R₃ is methyl, R₄ is H, R₅ is OH, X is O, and both ----- are a double bond.

63. (Previously amended) The method of claim 47 wherein the compound is a compound of formula (III):



64. (Original) The method of claim 63 wherein R_1 is halogen, CN, NO_2 , trifluoromethyl or OH.
65. (Original) The method of claim 63 wherein R_1 is OH.
66. (Original) The method of claim 63 wherein R_2 is (=O).
67. (Original) The method of claim 63 wherein R_3 is H or $(\text{C}_1\text{-C}_{10})$ alkyl.
68. (Original) The method of claim 63 wherein R_3 is methyl.
69. (Original) The method of claim 63 wherein R_4 is H or $(\text{C}_1\text{-C}_{10})$ alkyl.
70. (Original) The method of claim 63 wherein R_4 is H.
71. (Original) The method of claim 63 wherein R_5 is halogen, CN, NO_2 , trifluoromethyl or OH.
72. (Original) The method of claim 63 wherein R_5 is OH.

73. (Original) The method of claim 63 wherein X is O or S.
74. (Original) The method of claim 63 wherein X is O.
75. (Original) The method of claim 63 wherein both ----- are a single bond.
76. (Original) The method of claim 63 wherein one ----- is a double bond.
77. (Original) The method of claim 63 wherein both ----- are a double bond.
78. (Original) The method of claim 63 wherein R₁ is OH, R₂ is (=O), R₃ is methyl, R₄ is H, R₅ is OH, X is O, and both ----- are a double bond.
79. (Currently amended) The method of claim 1, ~~13, 14, 15, 15~~ or ~~17~~ 87 wherein the agent inhibits the activation of ubiquitin, the transfer of ubiquitin to the ubiquitin carrier protein, ubiquitin ligase, or a combination thereof.
80. (Currently amended) The method of claim 1, ~~13, 14, 15, 15~~ or ~~17~~ 87 wherein the agent inhibits ubiquitin ligase.
81. (Currently amended) The method of claim 1, ~~13, 14, 15, 15~~ or ~~17~~ 87 wherein the agent is a compound of formula (IV):



wherein R is hydrogen, an amino acid, or a peptide, wherein the N-terminus amino acid can optionally be protected at the amino group with acetyl, acyl, trifluoroacetyl, or benzyloxycarbonyl; A is an amino acid or a direct bond; A₁ is an amino acid; and R₁ is hydroxy or an amino acid, wherein the C-terminus amino acid can optionally be protected at the carboxy group with (C₁-C₆)alkyl, phenyl, benzyl ester or amide (e.g., C(=O)NR₂, wherein each R is independently hydrogen or (C₁-C₆)alkyl);

or a pharmaceutically acceptable salt thereof.

82. (Original) The method of claim 81 wherein the agent is H-Leu-Ala-OH, H-His-Ala-OH, or a combination thereof.

83. (Currently amended) The method of claim 1, ~~13, 14, 15, 16~~ or ~~17~~, 87 further comprising administering a second agent that enhances the activity of the agent.

84. (Original) The method of claim 83 wherein the second agent is EGTA.

85. (Currently amended) The method of claim 1 or 87 wherein the agent is an ubiquitin ligase inhibitor.

86. (Currently amended) The method of claim 1 or 87 wherein the agent alters endosomal processing.

87. (New) A method to identify an agent that alters adeno-associated virus (AAV) transduction of a mammalian cell, comprising:

- a) contacting the mammalian cell with an agent and virus;
- b) detecting or determining whether the agent alters viral transduction; and
- c) identifying whether the agent alters transduction after viral binding to the cell membrane and before synthesis to an expressible form of the viral genome.